Calcium intake and colorectal adenoma in a US colorectal cancer early detection program[1–3]

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ABSTRACT

Background: Calcium can reduce the risk of colorectal tumors by binding secondary bile and fatty acids, which leads to antiproliferative effects in the bowel, or by acting directly on the colonic epithelium, which affects differentiation and apoptosis.

Objective: We investigated calcium intake and risk of colon adenoma to evaluate the association of calcium intake with early stages of colorectal tumor development.

Design: We compared the supplemental and dietary calcium intakes of 3696 participants with histologically verified adenoma of the distal colon (ie, descending colon, sigmoid colon, or rectum) with the calcium intakes of 34 817 sigmoidoscopy-negative control participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Calcium intake was assessed at study entry with a 137-item food-frequency questionnaire and additional questions on the amount and duration of calcium supplement use.

Results: After adjustment for known risk factors, adenoma risk was lower by 12% for participants in the highest quintile of total calcium intake (>1767 mg/d) than for participants in the lowest quintile (<731 mg/d) (odds ratio: 0.88; 95% CI: 0.76, 1.02; *P* for trend = 0.04). The protective association between total calcium and colorectal adenoma was largely due to calcium supplement use, with a 27% decrease in adenoma risk for participants taking >1200 mg/d than for nonusers of supplements (odds ratio: 0.73; 95% CI: 0.56, 0.91; *P* for trend = 0.005). The protective associations of total and supplemental calcium were strongest for colon adenoma (descending and sigmoid colon).

Conclusion: High calcium intake, particularly from supplements, is associated with a reduced risk of distal colorectal adenoma. *Am J Clin Nutr* 2004;80:1358–65.

KEY WORDS   Colorectal adenoma, calcium, supplements, nutritional epidemiology

INTRODUCTION

Abundant evidence shows that colorectal carcinogenesis is a multistage process characterized by the successive accumulation of cancer-related gene mutations that are associated morphologically with the development of adenomatous polyps of increasing degrees of dysplasia, culminating in malignant invasion (1–3). Primary prevention by dietary and chemopreventive approaches that affect colorectal tumor progression in the earlier stages of this process could substantially reduce the colorectal cancer burden.

Calcium can reduce risk of colorectal tumors by binding bile and fatty acids in the bowel, thus reducing exposure of colonic epithelium to these potentially carcinogenic compounds (4) or by acting directly on colonic epithelium, influencing cellular differentiation, apoptosis, and associated proliferative activity, probably mediated by the calcium-sensing receptor (5, 6). Through 1998, reviewers concluded that calcium intake was not associated in epidemiologic studies with lower risk of colorectal adenoma or cancer (7–9). More recently, however, many studies showed protective associations (10–29) as have 3 randomized trials evaluating calcium supplementation and adenoma recurrence (30–32).

We investigated the association between calcium and colorectal adenoma in >3600 patients with distal adenoma and 34 000 sigmoidoscopy-negative participants in the screening arm of a randomized controlled trial. The large study size and detailed questions about calcium use enabled us to investigate these associations in detail, including specific attention to risks by diet compared with supplemental sources and risks by site, adenoma number, and histologic characteristics.

SUBJECTS AND METHODS

The National Cancer Institute is evaluating selected screening procedures for the early detection of prostate, lung, colorectal, and ovarian cancer (PLCO Trial) at 10 centers in the United States (Birmingham, AL; Denver; Detroit; Honolulu; Marshfield, WI; Minneapolis; Pittsburgh; Salt Lake City; St Louis; and Washington, DC) (33). At study entry, flexible sigmoidoscopic visualization of the distal colon (60 cm) was done on participants in the screening group. If the sigmoidoscopic examination was

suspicious for neoplasia (polyp or mass), participants were referred for endoscopic follow-up, including histopathologic examination. All available pathology reports on the removed lesions were obtained and coded by trained medical abstractors. Questionnaire data and biological samples were acquired from participants to study early markers and risk factors for cancer (33–35). Participants provided written informed consent. The study was approved by the institutional review boards of the National Cancer Institute and the 10 screening centers.

Study population

Between September 1993 and July 2001, 57 569 men and women aged 55–74 y had an initial successful sigmoidoscopic screening examination (insertion to at least 50 cm, with >90% of mucosa visible or suspect lesion found); 52 143 participants (90.6%) also provided risk factor and dietary information. We investigated 44 572 participants after excluding 7571 for self-reported history of cancer (except basal cell cancer; $n = 2363$); self-reported history of ulcerative colitis, Crohn disease, familial polyposis, colorectal polyps, or Gardner syndrome ($n = 4664$); extreme high or low energy intake (lowest and highest 1% on sex-specific energy intake; $n = 998$); or missing >7 items in the food-frequency questionnaire (FFQ; $n = 436$). Some participants were excluded for more than one reason.

We focused on the distal colon (including the descending and sigmoid colon and the rectum) because the screening examination covered only the distal colon. Of the 44 572 participants, 34 817 had no distal colon lesions suspicious for neoplasia. These participants formed the control group and were compared with 3696 case subjects with pathologically verified distal adenomatous polyps. Participants were ineligible for this study if they had hyperplastic polyps only ($n = 1499$), benign lesions not further specified ($n = 109$), colorectal lesions of unknown location ($n = 276$), polyps of uncertain histology or cancer ($n = 1526$), indeterminate screening results ($n = 37$), or positive screening but no follow-up endoscopy ($n = 2612$, of which $n = 1839$; 70.0% had a polyp < 5 mm). Data for this analysis were last updated in June 2003.

Data on calcium intake and other risk factors

At study entry, participants completed a risk factor questionnaire about sociodemographic factors, smoking history, use of selected drugs, disease history, family history of cancer, recent history of screening examinations, and physical activity. We assessed usual dietary intake over the past 12 mo before enrollment by using a 137-item FFQ (36) modified from the Willet and Block FFQs, which are widely used in the United States (13, 15–17, 30). Most participants completed the FFQ before (28.2%) or at the same day of sigmoidoscopy screening (56.1%). Portion size was queried for all food items except fruit and vegetables. Nutrient values for the FFQ database were calculated according to the method developed by Subar et al (37), which uses national dietary survey data and the nutrient database from US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (38). These dietary survey data were also used to calculate sex-specific portion sizes for participants aged >50 y. Then, by using individual responses on the FFQ, we calculated daily intake of nutrients by multiplying the daily frequency of each food item by its nutrient values. The FFQ also addressed multivitamin, single vitamin, and mineral supplement

use with questions about current use, past use (2 and 5 y ago), dosage, and years of intake. Supplemental calcium intake was calculated by summing the intake from calcium supplements (calcium, dolomite, Tums, and so forth; specific dose was assessed) and multivitamins (162 mg calcium per One-A-Day multivitamin pill, 0 mg calcium for any other multivitamin type), as defined by the generic multivitamins most frequently reported by participants aged 55–74 y in the third National Health and Nutrition Examination Survey cohort (39). If not otherwise specified, analysis of supplemental calcium was conducted for recent intake (0–2 y before enrollment). Total calcium intake was the sum of dietary and recent supplemental calcium intake.

Statistical analysis

We used the Wilcoxon nonparametric test to test differences in mean calcium intake between case and control subjects. Prevalence odds ratios (ORs) and associated 95% CIs were calculated by logistic regression analysis for quintiles of total and dietary (dairy and nondairy) calcium intake, based on the intake distribution of control participants. Because supplemental calcium is taken in particular doses, categories of intake were based on dosage groups (0, >0–400, >400–800, >800–1200, >1200 mg/d) rather than quintiles.

We calculated ORs with a basic statistical model, adjusting for age, sex, screening center, and energy intake [kcal/d, standard method for energy adjustment (40)]. To account for other potential confounders, which were selected according to a priori hypotheses for colorectal adenoma and cancer risk factors, we also calculated a multivariate model, controlling for the additional factors of ethnicity (American Indian or Alaskan Native, Asian, Hispanic, non-Hispanic black, non-Hispanic white, or Pacific Islander), educational attainment (<8 y school, 8–11 y school, 12 y school or high school equivalent, post–high school other than college, some college, college graduate, or postgraduate), tobacco use (never, smoked cigar or pipe, quit smoking 20+ years and smoked ≤1 pack/d, quit 20+ years and smoked >1 pack/d, quit <20 y and smoked ≤1 pack/d, quit <20 y and smoked >1 pack/d, or unknown), alcohol use (<1, ≥1–15, >15–30, or >30 g/d), use of aspirin and ibuprofen separately (no regular use, <2, 2–3, 4, 8, 12–16, 30, or 60 per month), vigorous physical activity (none, <1, 1, 2, 3, or 4+ hours/wk), body mass index (calculated as kg/m^2), total folate intake (in μg/d), red meat intake (in g/d), and dietary fiber intake (in g/d).

Dietary calcium and supplemental calcium were adjusted for each other, as was calcium from dairy foods, nondairy foods, and supplements. We conducted stratified analyses to explore effect modification by sex; age at randomization; family history of colorectal cancer; body mass index; height; aspirin and ibuprofen use; smoking status; and intake of fat, cholesterol, and fiber. For site-specific analysis (colon and rectum) we excluded cases with adenomas in both colon and rectum. We estimated the P value for trend by using calcium intake as a continuous variable.

To assess risks by adenoma characteristics, we classified cases by size (<1 compared with ≥1 cm), histology (presence compared with absence of advanced histologic characteristics of high-grade dysplasia or villous, including tubulovillous, elements), and multiplicity (one compared with multiple adenomas). We used an extension of polytomous logistic regression model (41) that quantifies heterogeneity in calcium effect by each of the individual adenoma characteristics after controlling for confounding because of the association between calcium

TABLE 1
Distribution of demographic characteristics in cases and controls[1]

Characteristic	Cases ($n = 3696$)	Controls ($n = 34\,817$)	P
Age, mean (y)	63.5	62.7	<0.0001
Female (%)	35.9	48.9	<0.0001
Ethnicity (%)			
American Indian, Alaskan Native	0.2	0.2	0.94
Asian	2.1	4.1	<0.0001
Hispanic	1.6	1.5	0.64
Non-Hispanic black	3.6	3.8	0.44
Non-Hispanic white	92.2	89.9	<0.0001
Pacific Island	0.4	0.5	0.24
Attained education: some college-level education (%)	67.4	71.2	<0.0001

[1] All values other than age and sex were age- and sex-standardized. Total calcium intake is the sum of dietary calcium and supplemental calcium intakes.

intake and the other tumor characteristics. These heterogeneity parameters are reported as case–case ORs. All P values were 2-sided.

RESULTS

Case subjects were significantly older, less educated, less likely to be women, and more likely to be non-Hispanic white (**Table 1**). High calcium consumers exercised more, had significantly higher intake of aspirin and ibuprofen, smoked less, and reported higher intake of folate and fiber and lower intake of red meat (**Table 2**).

In the control group, dairy products were the main source of dietary calcium (53%; including 35% from milk). Cereals and bread were the main nondairy calcium sources (21% of nondairy calcium). Supplemental intake of calcium was common (56.4% in the control group).

Case subjects with colorectal adenoma reported less use of calcium supplements than did control subjects ($\bar{x}$: 233 ± 348
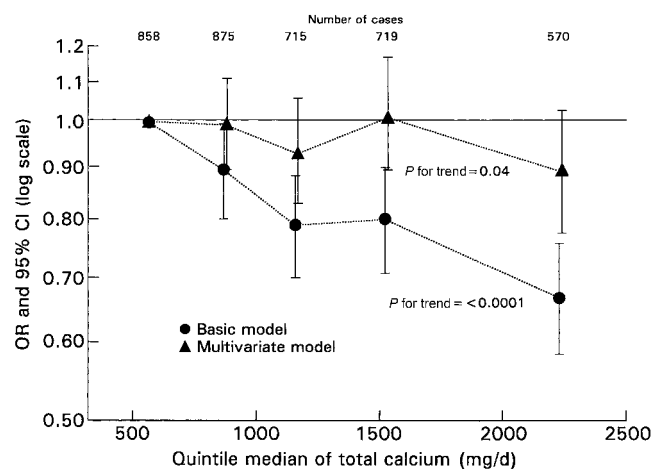

FIGURE 1. Association between total calcium intake and distal colorectal adenoma. Basic model adjusted for age, screening center, sex, and energy intake. Multivariate model adjusted for age, screening center, sex, energy intake, ethnic origin, educational attainment, tobacco use, alcohol intake, aspirin and ibuprofen use, physical activity, BMI, and intakes of red meat, folate, and dietary fiber. Total calcium intake is the sum of dietary calcium and supplemental calcium intake. The number of control subjects in quintiles 1–5 is 6963, 6964, 6963, 6964, and 6963, respectively. OR, odds ratio.

compared with 310 ± 398 mg/d, $P = $ <0.0001), but calcium intake from dietary sources was not different between case and control subjects (966 ± 481 compared with 971 ± 491 mg/d, $P = $ 0.68). Risks of distal adenoma decreased with increasing total calcium intake (supplemental plus dietary calcium) after adjustment for age, sex, center, and energy (P for trend < 0.0001; **Figure 1**). Adenoma risks were 35% lower [% change in relative risk = (1 − OR) × 100] for participants in the highest quintile of total calcium intake than for participants in the lowest quintile; further adjustment for several potential risk factors in a multivariate model resulted in weaker inverse associations (P for trend = 0.04), with modest risk reductions (12%) related to the highest quintile of calcium intake (OR: 0.88; 95% CI: 0.76, 1.02; $P = 0.09$).

TABLE 2
Distribution of study characteristics by quintiles of total calcium intake in controls[1]

Characteristic	Total calcium intake quintile[2]				Supplemental calcium intake		
	1 (lowest) ($n = 6928$)	3 ($n = 6928$)	5 (highest) ($n = 6928$)	P for trend	Nonusers ($n = 15\,164$)	Users ($n = 19\,673$)	P
BMI (kg/m²)[3]	27.4	27.3	27.1	<0.0001	27.6	27.0	<0.0001
Vigorous physical activity ≥ 1 h/wk (%)	55.5	65.2	72.1	<0.0001	61.9	67.4	<0.0001
Aspirin use > 1 time/wk (%)	34.1	39.1	41.3	<0.0001	37.2	46.2	<0.0001
Ibuprofen use > 1 time/wk (%)	15.2	17.1	22.1	<0.0001	17.5	21.5	<0.0001
Smoking status (%)							
Ever	57.5	53.1	51.3	<0.0001	53.7	53.5	0.76
Current	9.9	7.1	5.6	<0.0001	8.4	6.6	<0.0001
Alcohol ≥ 15 g/d (%)	20.8	21.8	20.7	0.44	20.8	21.4	0.25
Total caloric intake (kcal/d)[3]	1454	2092	2634	<0.0001	2038	2061	0.006
Red meat (g/d)[3]	91.6	79.5	60.2	<0.0001	80.8	73.5	<0.0001
Folate (μg/d)[3]	411	630	829	<0.0001	412	787	<0.0001
Fiber (g/d)[3]	21.5	23.8	25.3	<0.0001	22.9	24.0	<0.0001

[1] All values were age- and sex-standardized. Red meat, folate, and fiber intakes were also standardized for energy intake. Total calcium intake is the sum of dietary calcium and supplemental calcium intakes.

[2] Median total calcium in quintiles 1, 3, and 5: 572, 1171, and 2229 mg/d, respectively.
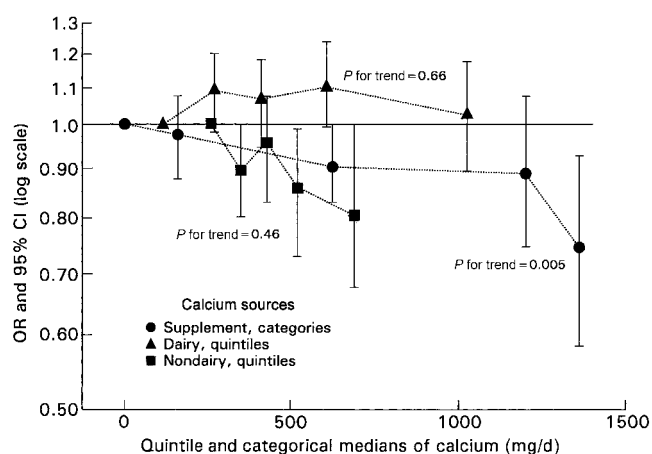
[3] Mean values.

FIGURE 2. Association between dairy, nondairy, and supplemental calcium intake and distal colorectal adenoma. OR and 95% CI adjusted for age, screening center, sex, energy intake, ethnic origin, educational attainment, tobacco use, alcohol intake, aspirin and ibuprofen use, physical activity, BMI, and intakes of red meat, folate, and dietary fiber. The number of case subjects in quintiles 1–5 of dairy calcium is 728, 785, 739, 758, and 686, respectively, and of nondairy calcium is 750, 705, 772, 717, and 752, respectively. The number of case subjects (control subjects) in categories 1–5 of supplemental calcium intake is 1911 (15 164), 889 (8369), 654 (7689), 155 (2115), and 87 (1480), respectively. OR, odds ratio.

Strong inverse associations and highly significant overall trends (P for trend < 0.0001) were also found in the basic model for dietary calcium overall and for dietary calcium from dairy and nondairy sources (data not shown); however, after adjustment for multiple covariates, neither association was significant (**Figure 2**). Compared with supplemental and dairy calcium, the range of

calcium intake from nondairy sources was relatively narrow (median intake for the lowest and highest quintiles, 261 and 688 mg/d, respectively; Figure 2).

In contrast to the inconsistent findings for calcium intake from dairy and nondairy sources, greater supplemental calcium use (0–2 y before enrollment) was associated with decreased adenoma risk in the basic model (P for trend < 0.0001) and after further multivariate adjustment (P for trend < 0.005) with 27% lower risk in participants taking >1200 mg/d compared with nonusers (OR: 0.73; 95% CI: 0.56, 0.91; Figure 2). Further adjustment for vitamin supplement intake (multivitamin and single-vitamin supplements) did not change the result (OR for taking > 1200 mg supplemental calcium/d compared with no supplemental calcium intake: 0.74; 95% CI: 0.58,0.95). Protection from colorectal adenoma was also shown for supplement use 5 y before enrollment in the study (multivariate OR: 0.79; 95% CI: 0.64, 0.96, comparing intake of >1200 mg/d with nonuse). Furthermore, continuous supplemental intake for duration of ≥ 10 y was associated with a smaller decrease in adenoma risk (multivariate OR: 0.89; 95% CI: 0.79, 1.00, comparing calcium intake ≥ 10 y with nonuse).

Calcium supplement users had reduced risks of adenoma of the colon (including the descending and sigmoid colon, P for trend $= 0.03$), showing a 30% lower risk in the highest supplement intake category than nonuse in the multivariate-adjusted model (**Table 3**); however, no association was found with rectal adenoma. Total calcium intake from supplements and diet showed a similar pattern of association for colon and rectal adenoma, but overall patterns of protection were not significant.

For total calcium intake we found a tendency for a stronger protective associations for large adenomas than for small adenomas ($P = 0.07$) and for multiple adenomas than for single

TABLE 3
Association between calcium intake and distal colorectal adenomas stratified by site[1]

	Quintile and defined categories					
	1[2]	2	3	4	5	P for trend
Total calcium (quintiles)						
Median (mg/d)	572	875	1171	1536	2229	
Colon adenoma						
No. of cases	588	557	466	480	383	
Odds ratio (95% CI)[3]	1.00	0.98 (0.86, 1.11)	0.88 (0.77, 1.02)	0.99 (0.86, 1.15)	0.87 (0.73, 1.02)	0.18
Rectal adenoma						
No. of cases	139	152	146	141	110	
Odds ratio (95% CI)[3]	1.00	1.11 (0.87, 1.42)	1.15 (0.89, 1.49)	1.19 (0.90, 1.58)	1.01 (0.73, 1.39)	0.15
Supplemental calcium (defined categories)						
Median (mg/d)	0	162	623	1200	1366	
Colon adenoma						
No. of cases/controls	1270/15 164	607/8363	424/7689	111/2115	55/1480	
Odds ratio (95% CI)[3]	1.00	0.97 (0.86, 1.09)	0.89 (0.78, 1.01)	0.98 (0.79, 1.22)	0.70 (0.52, 0.94)	0.03
Rectal adenoma						
No. of cases/controls	338/15 164	155/8363	147/7689	28/2115	20/1480	
Odds ratio (95% CI)[3]	1.00	0.97 (0.77, 1.21)	1.07 (0.85, 1.34)	0.77 (0.52, 1.20)	0.85 (0.52, 1.40)	0.55

[1] Total calcium intake is the sum of dietary calcium and supplemental calcium intakes. Categorical cutoffs for total calcium intake were 731, 1021, 1331, and 1767 mg/d, respectively, and for supplemental calcium intake were 0, 400, 800, and 1200 mg/d, respectively. Colon adenoma is defined as an adenoma in the descending and sigmoid colon. Cases with adenomas in both the rectum and colon were excluded.

[2] Reference category.

[3] Adjusted for age, screening center, sex, energy intake, ethnic origin, educational attainment, tobacco use, alcohol intake, aspirin and ibuprofen use, physical activity, BMI, and intakes of red meat, folate, and dietary fiber.

TABLE 4
Case-case odds ratios for distal colorectal adenoma characteristics in relation to calcium intake[1]

Adenoma characteristic	Total calcium		Supplemental calcium	
	Odds ratio (95% CI)[2]	P	Odds ratio (95% CI)[2]	P
	per 500 mg Ca/d		*per 500 mg Ca/d*	
Size, large vs small (*n* = 1063/2633)[3]	0.92 (0.84, 1.01)	0.07	0.96 (0.84, 1.10)	0.54
Histology, advanced vs nonadvanced histology (*n* = 891/2805)[4]	1.05 (0.95, 1.15)	0.36	0.94 (0.82, 1.09)	0.42
Multiplicity, multiple vs single (*n* = 900/2796)[5]	0.91 (0.83, 1.00)	0.05	0.94 (0.82, 1.08)	0.42

[1] Total calcium intake is the sum of dietary calcium and supplemental calcium intakes.

[2] Adenoma characteristics (size, histology, and multiplicity) are adjusted for each other. Odds ratios further adjusted for age, screening center, sex, energy intake, ethnic origin, educational attainment, tobacco use, alcohol intake, aspirin and ibuprofen use, physical activity, BMI, and intakes of red meat, folate, and dietary fiber.

[3] Large, ≥1 cm; small, <1 cm.

[4] Advanced histology is defined as either high-grade dysplasia or villous elements (including tubulovillous adenomas).

[5] Single one distal adenoma or multiple ≥2 distal adenomas.

adenomas ($P = 0.05$) (**Table 4**; note that the case–case ORs present differences in the strength of the calcium–adenoma association between adenoma characteristics and not main effects of calcium on adenoma subtypes, as described in "Subjects and Methods"). The protective associations of supplemental calcium did not vary significantly by adenoma size, histologic characteristics, or number.

Calcium supplement use was less common in men (42.4%) than women (71.1%). However, the association between supplemental calcium intake and adenoma risk did not significantly vary by sex (*P* for interaction of sex = 0.89). Furthermore, the sex-specific risk estimates for calcium from diet, dairy products, and nondairy foods were not different from the risk estimates for both sexes combined (data not shown).

Additional adjustment for vitamin D intake from supplements and diet did not substantially alter the association between calcium intake and adenoma risk (multivariate OR highest compared with lowest quintile total calcium: 0.91; 95% CI: 0.78, 1.06; *P* for trend = 0.12; multivariate OR comparing supplemental intake of >1200 mg/d with nonuse: 0.75; 95% CI: 0.58, 0.95; *P* for trend = 0.02). Furthermore, multivariate-adjusted associations for total and supplemental calcium intake with colorectal adenoma risk were not different across subgroups defined by age, family history of colorectal cancer, body mass index, height, aspirin and ibuprofen use, smoking, dietary fat intake, cholesterol intake, and fiber intake (data not shown). As single factors, tobacco use, dietary fiber, and folate intake were the strongest confounders. These 3 factors combined accounted for most of the attenuation of the calcium–adenoma associations seen in the multivariate models compared with the basic models (age, sex, center, and energy adjusted).

DISCUSSION

We found that greater calcium intake was related to reduced risk of colorectal adenoma. The associations were strongest for calcium from supplements and nondairy food sources and the decreases in risk were particularly pronounced for adenoma of the colon (descending and sigmoid colon).

Our findings for calcium supplements are consistent with 3 randomized clinical trials. Baron et al (30) found a significant 15% reduction in adenoma recurrence (*n* = 286 recurrent adenoma cases) after 4 y of calcium supplementation at 1200 mg/d,

and Bonithon-Kopp et al (31) found a 34% reduction in adenoma recurrence (*n* = 64 recurrent adenoma cases) after 3 y of supplementation at 2000 mg/d. Hofstad et al (32) found no association with adenoma growth in 116 polyp-bearing patients receiving a combination of antioxidants and calcium (1600 mg/d) for 3 y, but, consistent with the other 2 trials, they found a significant reduction in new adenoma formation in these polyp-bearing patients.

Our results for dietary calcium were less clear. Strong protective associations were found after adjustment for age, screening center, sex, and energy intake in the basic model, but, after multivariate adjustment, moderate protection was seen only with increased calcium from nondairy sources, not with calcium from dairy foods. Besides calcium and other potential anticarcinogenic components such as vitamin D, sphingolipids, and conjugated linoleic acid (42), milk and dairy products also contain components that possibly trigger the development of cancer, such as saturated fat or insulin-like growth factor I (43). Milk intake is also positively associated with circulating insulin-like growth factor I concentrations (44–46), which can enhance colonic epithelial cell proliferation (44, 47).

Recent epidemiologic evidence, however, points to a protective role for calcium in colorectal carcinogenesis regardless of calcium source. Through the mid-1990s, epidemiologic studies showed little association between calcium and colorectal adenoma or cancer (7–9), but about 20 more recent studies (10–29, 48, 49), including 8 cohort studies of colorectal cancer (10–17) and 2 case–control studies of almost 2000 colon cancer cases (22, 23), generally reported inverse associations between calcium intake and overall risk of colorectal tumors (10–29). In addition to the 3 randomized trials (30–32), supplemental calcium was related to reduced risk in most (11, 16, 17, 21, 22, 29, 50) but not all observational studies (25–27, 51). As recently shown in a meta-analysis, consumption of dairy products and, in particular, milk is consistently associated in epidemiologic studies with reduced risk of colorectal cancer (43).

Similar to our study, other studies observed a decreasing risk of colorectal adenoma and cancer with an increasing intake of calcium (14, 15, 17, 18, 22). However, such a linear trend was not found in all studies (16, 25), including a large cohort study observing no additional protection for colorectal cancer for calcium intake above 700–800 mg/d (16). Therefore, the preventive range of calcium intake remains less clear.

In our study the protective associations were strongest for tumors of the descending and sigmoid colon, with no association between calcium and rectal tumors. In other epidemiologic studies, associations between calcium intake and rectal tumors are equivocal, with some studies showing significant protective associations (17, 18, 52) with others showing statistically nonsignificant protective associations (25, 53) or no evidence of protection (11, 12, 49, 54–59). Our study focused on the distal (left side) colon, whereas other studies showed decreased risks of colorectal tumors with increasing calcium intake for the distal and proximal (right side) colon (22, 30, 50, 60) or restricted to the distal (16) or proximal colon (11, 31). These results caution a simple extrapolation of our findings to the proximal colon.

To ensure that the observed protective associations between calcium and adenoma risk were not confounded by other risk factors for colorectal tumors, we adjusted statistically for differences between case and control participants with respect to known and potential risk factors for colorectal tumors. However, the multivariate-adjusted models can bias the risk estimate because of errors related to each of the covariates and their intercorrelations (61), potentially accounting for part of the observed attenuation of risks compared with the basic model (62).

Only a few studies investigated the association of calcium intake with adenoma characteristics (30, 31, 63, 64). One study reported a stronger protective effect of supplemental calcium in relation to greater numbers of recurrent adenomas (30). Studies also found that calcium was either unrelated to adenoma size (<1 or ≥1 cm) (63, 64) or slightly more strongly associated with protection from small recurrent adenomas (<0.5 cm) compared with larger recurrent adenomas (≥0.5 cm) (30, 31). In our study multivariate analysis, including adenoma size, histology, and multiplicity as separate adenoma characteristics (41), shows no differential effect for calcium supplements by these 3 tumor characteristics but possibly a differential effect for total calcium by size and multiplicity. Our findings suggest that calcium can interfere with both the formation and progression of adenomas, although its precise role in adenoma natural history could not be directly assessed because we did not follow the longitudinal formation and progression of these lesions.

Vitamin D is involved in regulation of serum calcium concentrations, suggesting their potential interaction in colorectal tumor development. The largest intervention trial found that the preventive association between calcium supplementation and adenoma risk was strongest in subjects with high baseline serum vitamin D concentrations (65). In contrast, we did not find a substantial interaction between serum vitamin D and calcium intake that affected colorectal adenoma (66).

The estimated dietary calcium intake in this study population was slightly higher than that from the National Health and Nutrition Examination Survey III conducted in 1988–1994 (medians of 862 mg/d and 631 mg/d, respectively), which can possibly be explained by differences in dietary assessment (FFQ compared with 24-h recall) (67).

Despite a detailed calcium assessment, we cannot rule out misclassification resulting in an attenuated calcium–adenoma association, because accurate recall of dietary and supplemental intake might be difficult and intake assessed for the past year might not reflect the usual intake for the entire period of adenoma development. Differential recall of calcium intake between case and control subjects is less likely, because screening-detected, asymptomatic adenomas at this early preneoplastic stage are unlikely to affect dietary intake, and, furthermore, most participants (84.3%) filled out the questionnaire before or on the same day as the screening examination, which was before diagnosis. An advantage of the study design is that all participants were selected from the same source population (volunteers in a screening trial) and were screened with a standardized sigmoidoscopy procedure (ie, case subjects were not screened on the basis of symptoms). However, it is possible that distal lesions were missed by sigmoidoscopy, and participants were misclassified as control subjects, which would have likely weakened the calcium–adenoma association.

In selecting case and control subjects for this study, we excluded subjects with hyperplastic polyps only, tumors of unknown histology or location, cancer, or positive screening with no endoscopy follow-up. Because some subjects in these categories could arguably be legitimate case or control subjects, we carried out sensitivity analyses, assigning excluded subjects, respectively, to the case or control group. Our findings remained robust to these explorations, indicating that the exclusions did not bias our results.

In conclusion, in our large study, which included >3600 adenoma cases, we found an inverse association between calcium intake and risk of distal colorectal adenoma, in particular from nondairy foods and supplements and for adenoma of the distal colon. Our results are supported by a growing number of studies with different study designs, including cohort studies and intervention trials, which suggest that calcium intake provides moderate protection from colorectal adenoma.

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